UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF RESEARCH AND DEVELOPMENT
ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
CINCINNATI, OHIO 45268

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SUBJECT: Toxicity Information for Multiple Chemicals (Witco Chemical Site/Oakland, NJ)

FROM: Kenneth A. Poirier K.A. Poirier
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TO: John Osolin
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Region II

This memorandum is in response to a request submitted by Arlene Levin, of Alliance Technologies, for toxicity information for chemicals found at Witco Chemical Site.

Please note the guidance contained in this memorandum is a brief overview of existing risk assessment values and should not be used unless a complete package outlining the derivation of the risk assessment is provided to ECAO for review.

Attached please find the following information:

Attachment I: The attached table lists the chemicals provided and their requested oral RfD values.

Attachment II: Carcinogenicity information and classification.

Attachment III: Risk Assessment Issue Paper for: Status of Polyaromatic Hydrocarbons

Attachment VI: Supporting documentation for the toxicity values listed in the table.
a. 1,2,4-Trimethylbenzene
b. 4,4-DDD
c. Copper

Please feel free to contact ECAO at FTS 684-7300 if you have any further questions.

Attachments

cc: J. Dinan (OS-230)
P. Grevatt (Region II)
B. Means (OS-230)
A. Levin (Alliance Technology)

**Attachment I**

We have consulted the following sources: IRIS; the HEAST (Annual, FY 1991); the RfD, RfC, and CRAVE Work Group status tables and meeting notes; other EPA documents (e.g., DWCDs, WQCDs, and the DWHA); and ATSDR Toxicological Profiles.

## Carcinogen Slope Factors and Classifications

The oral slope factor for butyl benzyl phthalate is not available, the summary is available on IRIS. The oral slope factors for nickel and chromium(VI) are not available. However, several nickel compounds (nickel carbonyl, nickel refinery dust, and nickel subsulfide) and the summary for chromium(VI) are available on IRIS.

| Chemical | Classification |
|---|---|
| Trichlorofluoromethane | D |
| 1,2,4-trimethylbenzene | D[a] |
| 1,3,5-trimethylbenzene | D[a] |
| 4-nitrophenol | NA |
| Aluminum | NA |
| Antimony | NA |
| Barium | NA |
| Cobalt | NA |
| Iron | D[b] |
| Magnesium | NA |
| Vanadium | NA |
| Chromium (total) | D[a] |
| Chromium (VI) | NA |
| | A |

A = Human Carcinogen
D = Not Classifiable as to human carcinogenicity.
NA = No information available.

[a] U.S. EPA. 1987. Health Effects Assessment for Trimethylbenzenes. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Emergency and Remedial Response, Washington, DC

[b] U.S. EPA. 1991. Health Effects Assessment for Cobalt. (double check)

The classification of thallic oxide, thallium acetate, thallium carbonate, thallium chloride, thallium nitrate, thallium selenite, and thallium(I) sulfate is Group D (not classifiable as to human carcinogenicity).

**Attachment II**

| Chemical | Oral RfD (mg/kg/day) | |
|---|---|---|
| | Chronic | Subchronic |
| Aluminum | DI[a] | DI[a] |
| Cobalt | 1E-5[b] | NA |
| Copper | 1.3 mg/L[d]<br>3.7E-2[e] | 1.3 mg/L[d] |
| 4,4-DDE | ---[f] | ---[f] |
| 4,4-DDD | NA | NA |
| 1,3-Dichlorobenzene | 8.9E-2[g] | DI[h] |
| 1,4-Dichlorobenzene | 1E-1[g] | NA |
| Iron | Not requested | DI[a] |
| Magnesium | Not requested | NA |
| 4-Nitrophenol | UR | NA, DI[a] |
| Selenium | Not requested | 5E-3[k] |
| 1,2,4-Trimethylbenzene | DI[l] | DI[l] |
| 1,3,5-Trimethylbenzene | DI[l] | DI[l] |

DI - Data inadequate for quantitative risk assessment.
NA - Not available in sources searched.
UR - Under Review by the RfD/RfC Work Group (10/01/91).

a - Source: HEAST (Annual FY-1991, January 1991).
b - There has recently been a change in the assessment of cobalt. The information is currently under review and will be subject to extensive internal review, new information will be forthcoming.
d - Source: HEAST (Annual FY-1991, January 1991). This value is the current drinking water standard; the Drinking Water Criteria Document concluded toxicity data were inadequate for calculation of an RfD for copper.(U.S. EPA 1987)

U.S. EPA. 1987. Drinking Water Criteria Document for Copper. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC. External Review Draft.

e - This value was based on an assessment of incidental exposure to copper for the Iron Mountain site.

f - Please see attached supporting documentation (Attachment IV)

g - Source: DWHA (April 1991; RfD for o-, m- isomer is the same in the DWHA, whereas IRIS shows only 1,2-dichlorobenzene). HEAST (Annual FY-1991, January 1991) states that data are inadequate for 1,3-dichlorobenzene for quantitative risk assessment and also that the RfD for 1,4-dichlorobenzene is not determined.

h - Source: HEAST (Annual FY-1991; January 1991).

k - U.S. EPA. 1989. Health and Environmental Effects Document for Selenium and Compounds. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC. Based on a study by Yang et al., 1989.

Yang, G., S. Yin, L. Zhou, et al. 1989. Studies of safe maximal daily dietary Se-intake in a seleniferous area in China. II. Relation between Se-intake and the manifestation of clinical signs and cetain biochemical alterations in blood and urine. J. Trace Elem. Electrolytes Health Dis. 3: 123-130.

l - Source: HEAST (Annual FY-1991, January 1991). 1,2,4-Trimethylbenzene - please see attached supporting documentation; an oral RfD was not derived.

**Attachment III**

**Risk Assessment Issue Paper for:**
**Status of Polyaromatic Hydrocarbons**

## Toxicity Information

### I. RfDs/RfCs

**Oral**

Only 6 PAHs have interim oral RfDs. Table 1 lists the chemicals with oral RfDs along with the critical study, species, critical effect and reference dose. For the 5 chemicals that have been verified, the date of verification is listed, and the RfDs are available on IRIS.

**Inhalation**

Inhalation RfCs have not been calculated for any of the PAHs.

## Carcinogenic Assessment

### I. Background

The Office of Emergency and Remedial Response (OERR) is working on a draft approach for risk assessment of PAHs at Superfund sites. ECAO-Cin has been involved in the development of an ODW document for PAHs and is currently working on a Multimedia document for PAHs, both of which discuss toxicity equivalency factors for PAHs. There is presently no Agency position on this issue. It is likely that benzo[a]pyrene will serve as the reference point for TEF approaches to PAH risk assessments. The majority of PAH likely to be found in the environment appear to be less potent than benzo[a]pyrene. There are data, however, to indicate that methylated PAH and those containing oxygen and nitrogen may be more potent than benzo[a]pyrene.

### II. Slope Factors and Interim Approach

Benzo[a]pyrene has been classified as a B2, probable human carcinogen, however, there are no slope factors on IRIS. U.S. EPA (1980, 1984) derived an upper-bound oral slope factor of 11.5 per (mg/kg)/day using a linearized multistage procedure and the data of Neal and Rigdon (1967). U.S. EPA (1984) derived an upper-bound inhalation slope factor of 6.1 per (mg/kg)/day based on the data of Thyssen et al. (1981). These values could be adopted as interim values for the risk assessment of Superfund

Sites. While slope factors for other PAH compounds having a B2 classification are not available, OHEA suggests that benzo[a]pyrene estimates may be useful.

Carcinogen classifications for several PAHs that have been verified are listed below:

Acenaphthylene - D
Anthracene - D
Benz[a]anthracene - B2
Benzo[b]fluoranthene - B2
Benzo[k]fluoranthene - B2
Benzo[g,h,i]perylene - D
Chrysene - B2
Dibenz[a,h]anthracene - B2
Fluoranthene - D
Fluorene - D
Indeno[1,2,3-c,d]pyrene - B2
Naphthalene - D
Phenanthrene - D
Pyrene - D

The above classifications have been verified by the Carcinogen Risk Assessment Verification Endeavor (CRAVE) and risk assessment summaries can be found on IRIS.

**References:**

Neal, J. and R.H. Rigdon. 1967. Gastric tumors in mice fed benzo(a)pyrene - A quantitative study. Tox. Rep. Biol. Med. 25: 553-557.

NTP (National Toxicology Program). 1980. Unpublished subchronic toxicity study: Naphthalene (C52904), Fischer 344 rats. Prepared by Battelle's Columbus Laboratories under Subcontract No. 76-34-106002. March.

Thyssen, J., J. Althoff, G. Kimmerle and U. Mohr. 1981. Inhalation studies with benzo(a)pyrene in Syrian golden hamsters. J. Natl. Cancer Inst. 66: 575-577.

U.S. EPA. 1988. 13-week mouse oral subchronic toxicity study. Prepared by Toxicity Research Laboratories, LTD., Muskegon, MI for the Office of Solid Waste, Washington, DC.

U.S. EPA. 1989a. Mouse oral subchronic study with acenapthene. Study conducted by Hazelton Laboratories, Inc., for the Office of Solid Waste, Washington, DC.

U.S. EPA. 1989b. Subchronic toxicity study in mice with anthracene. Conducted by Hazelton Laboratories, Inc., for the Office of Solid Waste, Washington, DC.

U.S. EPA. 1989c. 13-week mouse oral subchronic toxicity study. Prepared by Toxicity Research Laboratories, LTD., Muskegon, MI for Office of Solid Waste, Washington, DC.

U.S. EPA. 1989d. Mouse oral subchronic toxicity with pyrene. Study conducted by Toxicity Research Laboratories, LTD., Muskegon, MI for the Office of Solid, Washington, DC.

**Attachment IVa**

## 1,2,4-Trimethylbenzene

Oral RfD

The U.S. EPA has prepared a Health Effects Assessment document on trimethylbenzenes (1987a) and a Drinking Water Health Advisory Document for 1,2,4-trimethylbenzene (1987b). We completed a TOXLINE search to determine if any additional information was published between 1986 and 1991. In addition, we also conducted a TSCATS search.

The U.S. EPA (1987a,b) determined that there was insufficient information for the derivation of a chronic RfD for 1,2,4-trimethylbenzene. No oral toxicity, developmental, or reproduction studies were discussed in the HEA or HA documents (U.S. EPA, 1987a,b). Several oral studies were identified from the TSCATS database. Litton Bionetics, Inc (1976) and MB Research Laboratories (1980) conducted LD50 studies. LD50s of 3550 and 3280 mg/kg were estimated in male and female Sprague-Dawley rats, respectively (Litton Bionetics, Inc., 1976). MB Research Laboratories estimated a higher LD50 (6000 mg/kg) in Wistar rats. Both studies reported observing inactivity in the rats dosed at levels as low as 1470 mg/kg. Effects observed at higher concentrations included incoordination, prostration, tremors, flaccid muscle tone, diarrhea, and emaciation.

In a nephrotoxicity study, groups of 10 male F-344 rats were administered 1,2,4-trimethylbenzene by gavage (neat) 500 or 2000 mg/kg 5 day/week for 4 weeks (EPL, 1983). A group of rats serving as controls were gavaged with saline. The only endpoint examined was kidney histopathology. Increased mortality (not significant) was observed at both doses. In the low dose group, 3/10 died; 2/10 in the high dose group died. Hyaline droplet nephropathy was observed in the 1,2,4-trimethylbenzene dosed rats, but the severity was the same as in the saline treated rats. This study could not be used as the basis for an RfD because of the limited number of endpoints examined.

Mobil Research and Development Corporation (1982) exposed groups of rats to a mixture containing toluene, ethylbenzene, o-, m-, and p-xylene; m-ethyltoluene; 1,2,4-trimethylbenzene; durene; and isodurene. Based on the AUC of 1,2,4-trimethylbenzene in the blood during the first 24 hours post-exposure, inhalation absorption was estimated to be 80-90%. As reported in the HEA (U.S. EPA, 1987a), 62.6% of a single oral dose of 1,2,4-trimethylbenzene was excreted as metabolites in the urine of male Wistar rats over a period of 3 days. Because only urinary excretion was monitored, it is possible that the more than 62.6% of the dose was absorbed from the gastrointestinal tract.

Below is a discussion of the derivation of an inhalation RfC for the mixture of 1,2,4- and 1,3,5-trimethylbenzene.

Data regarding the toxicity of trimethylbenzene are limited to one occupational study (Battig et al., 1958) and several subchronic inhalation studies in rats (Battig et al., 1958; Bernshtein, 1972; Wiglusz et al., 1975a,b). Of all of these studies, only Wiglusz et al. (1975a) was available for review; details of the others were obtained from secondary sources. Based on the available data, U.S. EPA (1987a) determined that the data were inadequate for derivation of a subchronic or chronic inhalation RfC. A provisional chronic inhalation RfC, with very low confidence, can be derived based on the occupational study by Battig et al. (1958). ACGIH (1986) recommended a TLV-TWA of 25 ppm based on this occupational study.

U.S. EPA (1987b,c) reported the results of the occupational study of Battig et al. (1958). In this study, an increase in toxic symptoms were found in 27 workers exposed for several years to "Fleet-X-DV-99", as compared to 10 unexposed controls (Battig et al., 1958). Clinical findings in the workers included central nervous system effects (vertigo, headaches, drowsiness), chronic, asthma-like bronchitis (classification criteria not reported), hyperchromic anemia (<4.5 million erythrocytes/$mm^2$) and disturbances in blood clotting. Fleet-X-DV-99 is a solvent containing 97.5% aromatic hydrocarbons (>30% 1,3,5-trimethylbenzene and >50% 1,2,4-trimethylbenzene) and 2.5% of paraffinic and naphthenic hydrocarbons. Rough quantitation of the exposure levels reported concentrations of hydrocarbon vapor ranging from 10-60 ppm.

U.S. EPA (1987a,b,c) reported the results of several subchronic inhalation studies in rats. Battig et al. (1958) exposed rats to 1700 ppm (n=8) Fleet-X-DV-99 solvent for 4 months or 500 ppm (number not specified) for 70 days (5 days/week, 8 hours/day). Four of the 8 rats exposed to 1700 ppm died within 2 weeks of exposure, while none of the animals in the 500 ppm died. Histological changes in the kidneys, liver, spleen and lung were reported in the rats exposed to 1700 ppm. Alterations in differential WBC counts (increase in the percentage of segmented neutrophilic granulocytes and a decrease in the percentage of lymphocytes) were reported at ≥500 ppm. Similar alterations in differential WBC counts as well as a significant elevation of SGOT levels were found in rats (n=6) exposed to 3.0 mg/L (610 ppm) 1,2,5-trimethylbenzene 6 hours/day, 6 days/week for 5 weeks (Wiglusz et al., 1975a,b). No exposure-related effects on hemoglobin levels and erythrocyte or leukocyte counts, or on the activity of SGPT,

glutamate dehydrogenase or ornithine carbamyl transferase were found in the Wiglusz et al. (1975a,b) studies. Bernshtein (1972) exposed rats to 1 mg/L (200 ppm) of a mixture of trimethylbenzenes 4 hours/day for 6 months. An inhibition of phagocytic activity of the leukocytes was reported. This study was summarized by Sandmeyer (1981) and further experimental details were not provided.

The Battig et al. (1958) study was used as the basis of a provisional RfC. The RfC was 2 x $10^{-2}$ mg/$m^3$ for the isomeric mixture of trimethylbenzenes. The RfC was derived from a LOAEL of 10 ppm (49 mg/$m^3$, assuming the solvent content to be exclusively trimethylbenzenes). A route-to-route extrapolation of this LOAEL could serve as the basis for an oral RfD. The LOAEL is adjusted to an equivalent continuous exposure level of 17.5 mg/$m^3$ by assuming occupationally exposed humans inhale 10 $m^3$/workday and 10 $m^3$ during the remainder of the day, and work 5 days/week. An equivalent dose of 5.0 mg/kg/day can be estimated from the equivalent continuous exposure concentration of 17.5 mg/$m^3$ by assuming humans weigh 70 kg and inhale 20 $m^3$/day. Pharmacokinetic data indicate that approximately 80% of an inhaled dose is absorbed (Mobil Research and Development Corporation, 1982) and at least 62.6% is absorbed orally (U.S. EPA, 1987a). An equivalent oral dose of 6.4 mg/kg/day is estimated by multiplying the equivalent inhaled dose by 0.8/.625, the ratio of the absorption efficiencies by the inhalation and oral routes, respectively.

$LOAEL_{ADJ}$ = 49 mg/m3 x (10 m3 /20 $m^3$) x (5 day/7 day)
= 17.5 mg/$m^3$

inhaled dose = 17.5 mg/$m^3$ x 20 $m^3$/day x 1/70 kg
= 5.0 mg/kg/day

oral dose = 5.0 mg/kg/day x (0.80 / 0.625)
= 6.4 mg/kg/day

Application of an uncertainty factor of 10,000 (10 for use of a LOAEL, 10 to extrapolate less than lifetime exposure, 10 for an inadequate database, and 10 to protect sensitive individuals) to the equivalent oral LOAEL yields a provisional RfD of 6 x $10^{-4}$ mg/kg/day. Confidence in the key study is low: few subjects were examined, the workers were exposed to other chemicals, including benzene, and the exposure level was estimated by quantifying the amount of hydrocarbon vapor present. Low confidence in the database reflects the lack of chronic, developmental or reproduction animal studies by any route of exposure and the poor quality of the available subchronic inhalation studies, and the limited amount of oral studies. Low confidence in the

provisional oral RfD follows.

Cancer slope factor

No information on the carcinogenicity of 1,2,4-trimethylbenzene was located on the update literature searches, in the HEA (U.S. EPA, 1987a) and the HA (U.S. EPA, 1987b). In addition, IARC has not reviewed the carcinogenicity data on this compound. Because no carcinogenicity data were located, U.S. EPA (1987a) placed 1,2,4-trimethylbenzene into weight-of-evidence classification group D.

**References:**


ACGIH (American Conference of Governmental Industrial Hygienists). 1986. Documentation of the Threshold Limit Values and Biological Exposure Indices. Fifth Edition. ACGIH, Cincinnati, OH. p. 608.

Battig, K., E. Grandjean, L. Rossi and J. Rickenbacher. 1958. No title provided. Arch. Gewerbepath. U. Gewerbehyg. 16:555 (Cited in U.S. EPA, 1987b,c).

Bernshtein, L.M. 1972. No title provided. Vopr. Gig. TR. Profzabol. Mater. Nauch. Konf. Vol. 53 (Cited in Sandmeyer, 1981).

EPL (Experimental Pathology Laboratories, Inc.). 1983. Four-week nephrotoxicity screening study in male F-344 rats. Pathology Report. FYI-AX-1283-0280.

Litton Bionetics, Inc. 1976. Acute oral toxicity study in rats: 1,2,4-trimethylbenzene. Final Report. OTS0514295.

MB Research Laboratories, Inc. 1980. Test for oral toxicity in rats. OTS0514286.

Mobil Research and Development Corporation. 1982. Bioavailability, bioaccumulation and elimination of 1,2,4-trimethylbenzene in the rat. OTS0206420.

Sandmeyer, E.E. 1981. Aliphatic hydrocarbons. In: Patty's Industrial Hygiene and toxicology, Vol. 3, G.D. Clayton and F.E. Clayton, Ed. John Wiley and Sons, Inc., New York. p. 3300-3302.

Wiglusz, R., M. Kienitz, G. Delag, E. Gllauszko and P. Mikulski. 1975a. Peripheral blood of mesitylene vapor treated rats. Bull. Inst. marit. Trop. Med. Gdynia. 26(3-4): 315-322.

Wiglusz, R., G. Delag and P. Mikulski. 1975b. Serum enzymes activity of mesitylene vapor treated rats. Bull. Marit. Trop.

Med. Gdynia. 26(3-4): 303-313. (Cited in U.S. EPA, 1987a).

U.S. EPA. 1987a. Health Effects Assessment for Trimethylbenzenes. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, D.C. ECAO-CIN-H095.

U.S. EPA. 1987b. Drinking Water Health Advisory for 1,2,4-Trimethylbenzene. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, D.C. ECAO-CIN-W029.

U.S. EPA. 1987c. Drinking Water Health Advisory for 1,3,5-Trimethylbenzene. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, D.C. ECAO-CIN-W030.

**Attachment IVb**

**DDT, DDD and DDE**

**Relative Toxicity of DDT and Isomers**

To provide an answer for this question, the IRIS files for DDT, DDD and DDE (U.S. EPA, 1990a), and the ATSDR Toxicological Profile for p,p'-DDT, p,p'-DDE and p,p'-DDD (ATSDR, 1989) have been reviewed. It should be emphasized that, due to time constraints, the primary research literature generally has not been consulted in this analysis. However, two reports of a study of the pharmacokinetics of DDT, DDD and DDE in humans (Roan et al., 1971; Morgan and Roan, 1971) and a report of a pharmacokinetic study in rats (Fawcett et al., 1987) have been reviewed as discussed later in this analysis.

IRIS and the ATSDR Profile indicate that there are limited data from studies of noncarcinogenic effects in animals or humans orally exposed to DDD or DDE alone. The HEA Summary Table A (U.S. EPA, 1990b) contains no entries for DDD or DDE. Oral RfDs for DDD and DDE apparently have not been reviewed or verified by the oral RfD work group.

A. Similarities among DDT, DDD and DDE

Review of information in the IRIS Carcinogenicity Assessments for DDT, DDD and DDE (U.S. EPA, 1990a) and in the ATSDR Toxicological Profile (1989) indicates that the three compounds display similarities. However, the uncertainties associated with the rationale for derivation by analogy are sufficient to warrant derivation of chemical-specific RfDs for each of the compounds.

Similarities among DDT, DDD and DDE include the following:

1. DDD and DDE are structurally similar to DDT and are both metabolic products of DDT in mice, rats and humans (U.S. EPA, 1990a; ATSDR, 1989). Hamsters, however, do not metabolize DDT to DDD or DDE (U.S. EPA, 1990a);

2. All three compounds have been classified to be Group B2 carcinogens; probable human carcinogens. In oral studies, positive results for liver tumors have been observed for one mouse strain treated with DDD, two strains of mice treated with DDE and two strains of mice treated with DDT. Increased incidences of liver tumors have been observed also in rats treated orally with DDT and in hamsters treated orally with DDE (U.S. EPA, 1990a);

3. Estimates of the potencies of each of the three compounds to cause liver tumors (i.e. slope factors) are practically identical: 3.4E-1/mg/kg/day for DDT (derived from rat and mouse data from six studies), 2.4E-1/mg/kg/day for DDD (derived from data for 1 mouse strain), and 3.4E-1/mg/kg/day for DDE (derived from hamster and mouse data from 3 studies) (U.S. EPA, 1990a).

The verified oral RfD for DDT (5E-4 mg/kg/day; U.S. EPA, 1990a) is based on a NOAEL (0.05 mg/kg/day, dietary for 27 weeks) for liver lesions in rats (hepatocellular hypertrophy, cytoplasmic oxyphilia and peripheral basophilic cytoplasmic granules) from a study by Laug et al (1950).

## B. Uncertainties associated with the use of the oral RfD for DDT as an RfD for DDD and DDE

A number of uncertainties are associated with the use of the oral RfD for DDT as an RfD for DDD and DDE. These uncertainties, as discussed below, suggest that enough toxicological and pharmacokinetic differences may exist among the three compounds to warrant derivation of specific RfDs for each. Further analysis, including examination of the primary research literature on DDD and DDE, will be required to determine if sufficient data of good quality are available to serve as the basis for RfDs for DDD and DDE.

1. Direct experimental verification that DDD and DDE will cause liver lesions similar to those caused by DDT at comparable dosage levels (and with similar thresholds) is lacking. As reviewed in the ATSDR (1989) Profile, only limited information exists regarding the hepatic effects of oral exposure of laboratory animals to DDD or DDE, but some of the data conflict with the hypothesis of identity among the abilities of DDT, DDD and DDE to cause hepatic toxic effects.

   In a 78-week dietary study of rats in which cancerous effects were not observed (NCI, 1978), hepatic necrosis was observed at dosage levels as low as 12 mg DDE/kg/day (a NOAEL for DDE was not identified), but neither DDD at up to 165 mg/kg/day nor DDT at 32 mg/kg/day caused hepatic alterations. In mice from the same study (NCI, 1978), neither DDE at 34 mg/kg/day nor DDD at 428 mg/kg/day caused noncancerous liver lesions, but DDT at doses as low as 2.86 mg/kg/day was associated with amyloid changes in the liver. Statistically significant increased incidences of liver tumors were noted for mice treated with DDE in this study, but not for those treated with DDT or DDD (NCI,

1978).

2. Data for the gastrointestinal absorption and elimination of DDT, DDD and DDE in humans and for the elimination of DDT, DDD and DDE from laboratory animals indicate that the pharmacokinetic behavior of these compounds may not be identical (ATSDR, 1989).

The ATSDR (1989) Profile cites reports (Morgan and Roan, 1971; Roan et al., 1971) of a study of humans comparing the absorption, storage and excretion of ingested DDT, DDD and DDE, but does not specify clearly whether the data indicate quantitative differences among the compounds. The original research reports have been examined and, although the study contained only a limited number of subjects, the data indicate that the pharmacokinetics for the three compounds are not identical in humans. Ingestion of DDT or DDD resulted in increased urinary excretion of p,p'-DDA (bis[p-chlorophenylacetic]acid, but ingestion of DDE did not. Elimination from adipose tissue following cessation of ingestion was fastest for DDD, intermediate for DDT and slowest for DDE. The authors also reported that, during the period of ingestion, rates of increases in DDE concentrations in serum and adipose tissues (per unit dose) were higher than comparable rates of increases in DDT concentrations during DDT ingestion.

In rats given a single intraperitoneal injection of 200 mg radiolabeled DDT, DDE or DDD/kg, the time required to excrete 50% of the administered radioactivity in urine and feces was 12 days for DDT, 24 days for DDE and 3 days for DDD (Fawcett et al., 1987).

In summary, although there are demonstrated similarities among the chemical structures and carcinogenicities of DDT, DDD and DDE, evidence is available to suggest that the noncarcinogenic toxicology and pharmacokinetic behavior of the three compounds may not be identical. These differences may be sufficient to preclude derivation of RfDs for DDD and DDE by analogy to DDT.

**REFERENCES:**

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Laug, E.P., A.A. Nelson, O.G. Fitzhugh and F.M. Kunze. 1950. Liver cell alteration and DDT storage in the fat of the rat induced by dietary levels of 1-50 ppm DDT. J. Pharmacol. Exp. Therap. 98:268-273. Cited in U.S. EPA, 1990a.

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NCI (National Cancer Institute). 1978. Bioassay of DDT, TDE and p,p'-DDE for possible carcinogenicity. NCI Report No. 131. DHEW Publ. No. (NIH) 78-1386. Cited in U.S. EPA, 1990a and ATSDR, 1989.

Roan, C., D. Morgan, E. Paschal. 1971. Urinary excretion of DDA following ingestion of DDT and DDT metabolites in man. Arch. Environ. Health 22:309-315.

U.S. EPA. 1990a. Integrated Risk Information System (IRIS). Online. Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH.

U.S. EPA. 1990b. Health Effects Assessment Summary Tables. Fourth Quarter. FY-1990. Office of Solid Waste and Emergency Response. Washington, DC.

**Attachment IVc**

## Risk Assessment Issue Paper for:

## Interim Oral RfD for Copper

The emetic properties of copper have been known for some time. There are several reports of gastrointestinal disturbances (e.g. vomiting, diarrhea, abdominal pain) in individuals consuming beverages contaminated with copper (ATSDR 1989). The lowest level that elicit a response was approximately 5 mg (0.07 mg/kg/day). Extensive hepatic centrilobular necrosis has also been observed in individuals intentionally consuming a single, large dose of copper sulfate (Chuttani et al. 1965). Two reports of health effects in humans exposed repeatedly to copper were discussed in the ATSDR profile (ATSDR 1989). The first report involved a family that drank copper contaminated water in the morning for approximately 1.5 years. Recurrent and acute episodes of nausea, vomiting and abdominal pain were reported. Samples of the morning water contained 7.8 mg/L copper (Spitalny et al. 1984). The second report involved 2 infant siblings exhibiting liver damage (hepatosplenomegaly, cirrhosis). The infants drank contaminated tap water (2-3 mg Cu/L) for ≤ 9 months (Mueller-Hoecker et al. 1988). It should be noted that children under 1 year of age are unusually susceptible to the toxicity of copper because homeostatic mechanisms for clearing copper from the body and regulating its gastrointestinal absorption have not fully developed at this age. Because both of these reports have a small sample size and actual water intakes were not reported, neither study is adequate for the derivation of an oral RfD.

Numerous animal subchronic studies which demonstrate the toxicity of copper in rats and pigs were reviewed by ATSDR (1989). The liver appears to be a primary target organ for copper toxicity. Hepatic centrilobular necrosis followed by regeneration was observed in rats administered ≥ 100 mg/kg/day. Alterations in serum enzymes (e.g. SGOT) which may be indicative of liver damage have been observed at dietary concentrations of approximately 40 mg/kg/day. A number of studies have demonstrated the development of tolerance to copper toxicity in rats and pigs (ATSDR 1989). It is not known if humans would also develop tolerance to copper toxicity, therefore it is not clear whether rats and pigs may serve as a good model for human copper toxicity.

In conclusion, in order to protect against the adverse health effects associated with copper deficiency the RfD for copper should be at least $2 \times 10^{-2}$ to $4 \times 10^{-2}$ mg/kg/day, a range considered as "safe and adequate" for copper intakes for adults (NAS, 1989). FAO/WHO expert committee on food additives

concluded that a copper intake (from dietary sources) as high as 0.5 mg/kg/day would not result in adverse health effects (FAO/WHO 1971). However, individuals drinking beverages contaminated with approximately 7 x $10^{-2}$ mg/kg/day exhibited signs of gastrointestinal disturbances. Thus, an interim RfD for copper should fall between 4 x $10^{-2}$ mg/kg/day and 7 x $10^{-2}$ mg/kg/day.

**REFERENCES:**

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TABLE 1

Oral RfDs for PAHs

| Compound/ Status | Exposure | Species | Critical Effect | Uncertainty Factor | Modifying Factor | Reference Dose | Reference |
|---|---|---|---|---|---|---|---|
| Acenapthene / Verified (11/15/89) | | | | | | | |
| | 175 mg/kg/day daily by gavage for 90 days (NOAEL); 350 mg/kg/day (LOAEL) | Mouse | Hepatotoxicity | 3000 | 1 | 6E-2 mg/kg/day | U.S. EPA, 1989a |
| Anthracene / Verified (11/15/89) | | | | | | | |
| | 1000 mg/kg/day daily by gavage for 90 days (NOEL) (HDT) | Mouse | No effects | 3000 | 1 | 3E-1 mg/kg/day | U.S. EPA, 1989b |
| Fluoranthene / Verified (11/15/89) | | | | | | | |
| | 125 mg/kg/day daily by gavage via corn oil for 13 weeks (NOAEL); 250 mg/kg/day (LOAEL) | Mouse | Nephropathy, increased relative liver weights, hematological and clinical effects | 3000 | 1 | 4E-2 mg/kg/day | U.S. EPA, 1988 |
| Fluorene / Verified (11/15/89) | | | | | | | |
| | Gavaged via corn oil 125 mg/kg/day for 13 weeks (NOAEL); 250 mg/kg/day (LOAEL) | Mouse | Decreased RBC, packed cell volume and hemoglobin | 3000 | 1 | 4E-2 mg/kg/day | U.S. EPA, 1989c |
| Napthalene | | | | | | | |
| | 50 mg/kg/day in diet for 5 days/week for 13 weeks (35.7 mg/kg/day) | Rat | Decreased body weight gain. | 10,000 | 1 | 4E-3 mg/kg/day | NTP study (1980) |

TABLE 1 (cont.)

Oral RfDs for PAHs

| Compound/ Status | Exposure | Species | Critical Effect | Uncertainty Factor | Modifying Factor | Reference Dose | Reference |
|---|---|---|---|---|---|---|---|
| Pyrene / Verified (11/15/89) | | | | | | | |
| | 75 mg/kg/day by gavage via corn oil for 13 weeks (NOAEL) | Mouse | Nephropathy and decreased kidney weight | 3000 | 1 | 3E-2 mg/kg/day | U.S. EPA, 1989d |

HDT = Highest Dose Tested